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ORIGINAL ARTICLE

Impact of single-agent daily prednisone on outcomes in men with metastatic castration-resistant prostate cancer

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BACKGROUND: Despite palliative benefits and PSA responses, the objective clinical impact of daily oral prednisone (P) for metastatic castration-resistant prostate cancer (mCRPC) is unknown. We performed a pooled analysis of control arms of randomized trials that either did or did not administer single-agent P to evaluate its impact on overall survival (OS) and toxicities.
METHODS: Individual patient data from control arms of randomized trials of men with mCRPC who received placebo or P+placebo post docetaxel were eligible for analysis. The impact of P on OS and severe toxicities was investigated in Cox regression models adjusted for known prognostic factors. Statistical significance was defined as $P < 0.05$ and all tests were two sided.
RESULTS: Data from the control arms of two randomized phase III trials were available totaling 794 men: the COU-AA-301 trial ($n = 394$) administered P plus placebo and the CA184-043 trial ($n = 400$) administered placebo alone. P plus placebo was not significantly associated with OS compared with placebo in a multivariable analysis (hazard ratio = 0.89 (95% confidence interval 0.72–1.10), $P = 0.27$). Other factors associated with poor OS were Eastern Cooperative Oncology Group (ECOG)-performance status (PS) $\geqslant 1$, Gleason score $\geqslant 8$, liver metastasis, high PSA, hypoalbuminemia and elevated lactate dehydrogenase (LDH). Grade $\geqslant 3$ therapy-related toxicities were significantly increased with P plus placebo compared with placebo (hazard ratio = 1.48 (95% confidence interval 1.03–2.13), $P = 0.034$). Other baseline factors significantly associated with a higher risk of grade $\geqslant 3$ toxicities were ECOG-PS $\geqslant 1$, hypoalbuminemia and elevated LDH. Fatigue, asthenia, anorexia and pain were not different based on P administration.
CONCLUSIONS: P plus placebo was associated with higher grade $\geqslant 3$ toxicities but not extension of OS compared with placebo alone in men with mCRPC who received prior docetaxel. Except for the use of P with abiraterone to alleviate toxicities, the use of P should be questioned given its association with toxicities and resistance.

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INTRODUCTION

Since randomized trials employed daily low-dose oral prednisone (P) with mitoxantrone chemotherapy to treat men with metastatic castration-resistant prostate cancer (mCRPC), P has been used subsequently in combination with taxanes.[1–5] P was combined with abiraterone acetate to mitigate the toxicities of mineralocorticoid excess.[6,7] However, the impact of single-agent daily P on clinical outcomes remains unclear.

Moreover, P may induce toxicities, exacerbate comorbidities, incite resistance pathways and attenuate the benefits of immunotherapy.[8,9] Daily corticosteroids may cause hyperglycemia, osteoporosis, myopathy, edema, hypertension and infections and potentially counteract the benefits of immunotherapy. In the era of emerging promising immunotherapeutic agents, long-term therapy with corticosteroids preceding or following the immunotherapeutic is not desirable. In this context, abiraterone plus P did not blunt the immunologic properties of sipuleucel-T in a randomized phase II trial, although the impact on long-term outcomes is unknown.[10] In addition, prolonged administration of daily corticosteroids may promote steroid dependency, and withdrawal may lead to adverse effects of low cortisol such as fatigue and postural hypotension.[11] Therefore, a reevaluation of the role of daily oral corticosteroids is overdue.

One trial-level meta-analysis of randomized trials could not demonstrate a significant impact of P, mostly in combination with chemotherapy, on overall survival (OS) or toxicities.[12] However, the impact of single-agent P on OS and toxicities is unknown. Indeed, a randomized trial comparing P with placebo is unlikely to be ever performed. We performed a comparative analysis of control arms of two randomized trials that either did or did not administer single-agent P to evaluate its impact on OS and severe toxicities.

MATERIALS AND METHODS

Trials and patients

Individual patient data from the control arms of the CA184-043 and COU-AA-301 phase III trials were available for analysis.[6,13] Both trials were designed for men with mCRPC with progressive disease following docetaxel. CA184-03 compared ipilimumab with placebo as a 90 min intravenous infusion every 3 weeks up to 4 doses. All patients also received a single 8 Gy dose of radiotherapy to a bone lesion before beginning the intravenous therapy. COU-AA-301 compared oral P 5 mg twice daily combined with either abiraterone acetate or placebo. Men in the control arm of CA184-043 received placebo only and corticosteroids were not allowed at baseline but were allowed subsequently if clinically necessary (for example, for patients judged to have severe immune adverse events). Those in the COU-AA-301 received daily P plus placebo. Both trials recruited men with mCRPC who had previously received docetaxel. Demographic data, clinical and

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Table 1. Patient characteristics and outcomes

Characteristic	*Statistic*	*CA184-043*		*COU-AA-301*		P-*value*
		N	*Result*	N	*Result*	
Baseline characteristics						
Age	Mean (s.d.)	400	67 (8)	394	69 (9)	0.001
	Median (IQR)		68 (62–73)		69 (63–75)	
ECOG-PS	0	390	170 (44)	381	137 (36)	0.033[a]
	1		220 (56)		199 (52)	
	2		0 (0)		45 (12)	
Gleason score	*N* (%) 8–10	375	186 (50)	395	205 (52)	0.52
Baseline albumin (g dl^{-1})	Median (IQR)	359	4.1 (3.9–4.3)	393	4.1 (3.8–4.3)	0.059
Lymphocytes $\times 10^3$ μl^{-1}	Median (IQR)	349	1.2 (0.9–1.7)	363	1.1 (0.8–1.5)	0.003
Neutrophils $\times 10^3$ μl^{-1}	Median (IQR)	349	4.3 (3.2–5.8)	363	4.4 (3.4–6.1)	0.13
NL ratio	Median (IQR)	349	3.6 (2.4–5.3)	363	4.3 (2.8–6.6)	<0.001
	N (%) $\geqslant 5$		95 (27)		138 (38)	0.002
PSA	Median (IQR)	334	177 (47–417)	391	132 (40–474)	0.74
LDH	*N* (%) $>$ULN	378	214 (57)	382	165 (43)	<0.001
Hemoglobin	*N* (%) Anemic (<11 g dl^{-1})	380	111 (29)	376	116 (31)	0.63
Bone metastases	*N* (%)	400	364 (91)	398	358 (90)	0.61
Visceral metastases	*N* (%)	400	114 (29)	397	101 (25)	0.34
Liver metastases	*N* (%)	400	47 (12)	397	30 (8)	0.055
Survival						
N (%) deaths	*N* (%)	400	351 (88)	394	224 (57)	
Overall survival	Median (95% CI) months	400	10 (8–11)	398	11 (10–12)	0.35[b]
	1 Year (95% CI) %		72 (67–76)		78 (73–82)	0.12[c]
	2 Years (95% CI) %		41 (36–46)		45 (40–50)	

Abbreviations: CI, confidence interval; ECOG-PS, Eastern Cooperative Group-Performance Status; IQR, interquartile range; LDH, lactate dehydrogenase; NL, neutrophil/lymphocyte; ULN, upper limit of normal. [a]Comparison is ECOG 0 versus ECOG $\geqslant 1$. [b]Log-rank test. [c]Wilcoxon test.

laboratory prognostic factors, OS and toxicity data were collected. Toxicities were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0) in both trials.

Statistical methods

The Kaplan–Meier method was used to calculate OS. The χ^2 and Wilcoxon rank sum tests were used to compare baseline differences. Given longer follow-up in the BMS (Bristol-Myers Squibb) CA184-043 trial, both a log-rank and generalized Wilcoxon test were performed. The generalized Wilcoxon test adds weights (relative to the number of patients still at risk), thereby putting greater emphasis on earlier OS times. Cox proportional hazards regression were used to explore effect of P on OS adjusted for potential prognosticators. Baseline prognostic factors available from both trials and previously reported to be prognostic factors were used in the multivariable analysis including the following: age, Eastern Cooperative Oncology Group (ECOG)-performance status (PS), Gleason score, PSA albumin, lymphocytes, neutrophils, sites of metastases (bone, liver, visceral), hemoglobin and lactate dehydrogenase (LDH).[14–16] Logistic regression was used to evaluate the association of grade $\geqslant 3$ adverse events overall regardless of attribution to therapy as well as attributed to therapy. Specific toxicities and events that may be alleviated by P were also examined for association of overall and grade $\geqslant 3$ events with treatment including fatigue, asthenia, anorexia and pain. Statistical significance was defined as a *P*-value of <0.05, and all tests were two sided.

Table 2. Grade $\geqslant 3$ AEs experienced by $>2.5\%$ (10 patients)[a]

Characteristic	*CA184-043*	*COU-AA-301*
Anemia	47 (11.8%)	30 (7.5%)
Asthenia	14 (3.5%)	8 (2.0%)
Anorexia	0	12 (3.0%)
Arthralgia	0	16 (4.0%)
Back pain	22 (5.5%)	38 (9.5%)
Bone pain	19 (4.8%)	29 (7.3%)
Decreased appetite	13 (3.3%)	1 (0.3%)
Dehydration	10 (2.5%)	7 (1.8%)
Dyspnea	8 (2.0%)	12 (3.0%)
Fatigue	37 (9.3%)	39 (9.8%)
Musculoskeletal pain	12 (3.0%)	8 (2.0%)
Nausea	7 (1.8%)	10 (2.5%)
Pain	24 (6.0%)	7 (1.8%)
Pain in extremity	11 (2.8%)	21 (5.3%)
Pelvic pain	2 (0.5%)	10 (2.5%)
Pulmonary embolism	4 (1.0%)	12 (3.0%)
Spinal cord compression	4 (1.0%)	20 (5.0%)
Vomiting	10 (2.5%)	11 (2.8%)
At least 1 grade $\geqslant 3$ AE	236 (59.0%)	243 (61.1%)
At least 1 grade $\geqslant 3$-attributable AE	43 (10.8%)	71 (17.8%)

Abbreviation: AE, adverse event. [a]Using National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0).

RESULTS

Patient characteristics

Data from all 798 patients enrolled in the control arm from either clinical trial were available for analysis, namely 400 from the placebo-alone group in CA184-043 and 398 from the P plus placebo group in COU-AA-301. Descriptive statistics are presented in Table 1, and frequently occurring grade $\geqslant 3$ adverse events are summarized in Table 2. There were statistically significant differences between the two trials for some baseline variables with higher age, lower LDH and poorer ECOG-PS in the COU-AA-301 patients, and lower neutrophil/lymphocyte ratio in the CA184-043 patients. A total of 32/304 (10.5%) evaluable CA184-043 patients had a decline in PSA of $\geqslant 50\%$ compared with baseline, as opposed to 40/317 (12.6%) of COU-AA-301 patients that was not statistically significant ($P=0.45$). Alternatively, no difference was seen in rates of PSA decline (32/400 = 8.0% versus 40/398 = 10.1%, $P=0.33$) if one considers all patients without postbaseline PSA as a failure to have a PSA response.

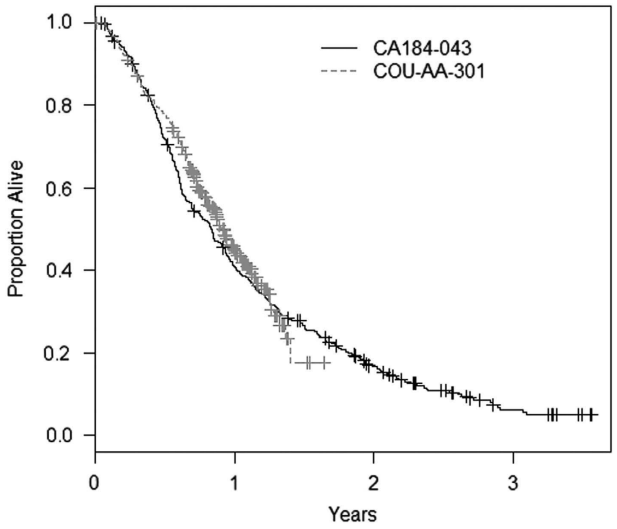

Figure 1. Association of prednisone with survival.

Table 3. Multivariable analysis of for association of variables with overall survival

Factor	*Type*	*Hazard ratio (95% CI)*	P-*value*
Age	Per 10 years older	1.10 (0.97–1.24)	0.13
ECOG-PS	⩾1 vs 0	1.29 (1.05–1.60)	0.017
Gleason score	⩾8 vs ⩽7	1.25 (1.02–1.52)	0.028
Liver metastases	Yes vs no	1.50 (1.03–2.16)	0.033
Visceral metastases	Yes vs no	1.06 (0.82–1.37)	0.65
Bone metastases	Yes vs no	1.35 (0.91–2.01)	0.13
PSA	Log-transform, per 1 unit increase	1.16 (1.09–1.23)	<0.001
Baseline albumin	Per 1 g dl^{-1} increase	0.50 (0.37–0.66)	<0.001
NL ratio	Log-transform, per 1 unit increase	1.16 (0.99–1.34)	0.063
LDH	Elevated vs normal	2.10 (1.71–2.57)	<0.001
Hemoglobin	<11 vs ⩾11 g dl^{-1}	1.14 (0.91–1.42)	0.27
Prednisone	P vs no P	0.89 (0.72–1.10)	0.27

Abbreviations: CI, confidence interval; ECOG-PS, Eastern Cooperative Group-Performance Status; LDH, lactate dehydrogenase; NL, neutrophil/lymphocyte; P, prednisone.

Association of P with OS

There was no significant difference in OS (median OS 10.0 vs 10.9 months, $P=0.12$ using Wilcoxon test) between the placebo-alone and placebo plus P groups. In the 610 patients with data available for all factors, the multivariable analysis also did not demonstrate a significant association ($P=0.27$) between P administration and OS (Figure 1 and Table 3). A supportive analysis performed with weights applied for the number of patients at risk and normalized to the sample size yielded similar results (univariable $P=0.37$ and multivariable $P=0.92$). Multiple previously known prognostic factors were significantly associated with poor OS on multivariable analysis including ECOG-PS ⩾1, Gleason score ⩾8, liver metastasis, PSA, albumin and LDH.

Association of P with toxicities

The proportion of patients with at least one grade ⩾3 adverse event was similar (59.0% versus 61.1%, χ^2 test $P=0.56$) in the placebo-alone and placebo plus P groups (Table 2 and Figure 2). Although P administration was not significantly associated with overall grade ⩾3 adverse events on univariable analysis, multivariable analysis demonstrated a significantly higher risk of grade ⩾3 toxicities ($P=0.034$). Upon further inspection, LDH was observed as a potential confounding variable. In patients with LDH >upper limit of normal (ULN), 81% had a grade ⩾3 adverse event in the COU-AA-301 trial compared with 69% in the CA184 trial, whereas for those with LDH <ULN, 47% and 46% had a grade ⩾3 adverse event in COU-AA-301 and CA184, respectively. Similarly, P administration was significantly associated with therapy-attributed grade ⩾3 toxicities on multivariable analysis ($P=0.001$) (Table 4a and b), but not univariable analysis.

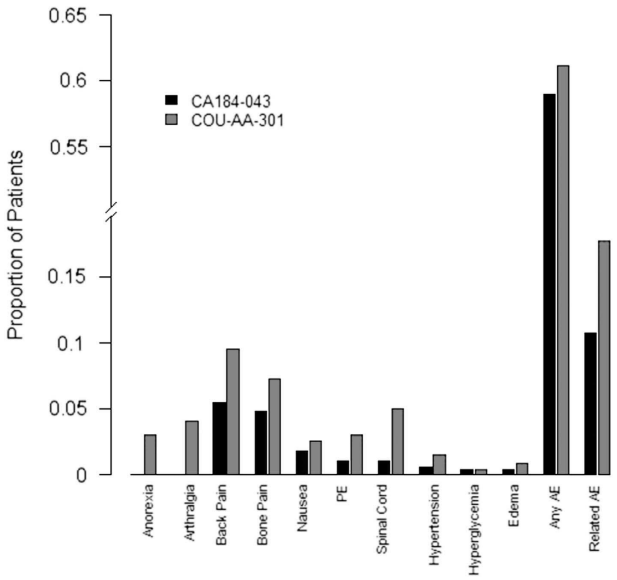

Figure 2. Frequency of grade ⩾3 toxicities with placebo or daily oral prednisone. Using the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0) in both trials. AE, adverse event; PE, pulmonary embolism.

When examining fatigue, asthenia, anorexia and pain that may be alleviated by P, both overall and grade ⩾3 events were not multivariably associated with P, except grade ⩾3 anorexia. Although limited by small numbers, there was a statistically significant difference in the proportion of patients with grade ⩾3 anorexia (12/398 (3.0%) with P plus placebo vs 1/400 (0.3%) with placebo alone, $P=0.002$, multivariable odds ratio = 11.48 (95% confidence interval 1.34–98.03), $P=0.026$).

DISCUSSION

In this large retrospective study of control arms of two phase III trials, P plus placebo was associated with higher grade ⩾3 toxicities (both overall and those attributed to therapy) but not extension of OS or PSA response compared with placebo alone after controlling for major baseline clinical and laboratory prognostic factors in post-docetaxel men with mCRPC. In addition, events of all grades that may be alleviated by P such as fatigue, asthenia, anorexia and pain did not appear significantly different based on P administration, suggesting the lack of clear palliative benefit. Our study included 798 patients overall and 610 were evaluable for the multivariable analysis that evaluated the independent impact of single-agent P after accounting for major baseline prognostic factors. These results partially accord with the previously reported trial-level meta-analysis of randomized trials that did not demonstrate a significant impact of P, generally in combination with chemotherapy, on OS or toxicities.[12]

Our study is limited by its retrospective design, and the fact that patients were not randomized between treatment arms. There

Table 4. Multivariable analysis of for association of variables with all grade ⩾3 toxicities (a) and toxicities attributable to therapy (b)

Factor	*Type*	*Odds ratio (95% CI)*	P-*value*
(a)			
Age	Per 10 years older	0.99 (0.79–1.24)	0.93
ECOG-PS	⩾1 vs 0	1.52 (1.06–2.18)	0.025
Gleason score	⩾8 vs ⩽7	1.41 (0.99–2.01)	0.059
Liver metastases	Yes vs no	1.15 (0.53–2.53)	0.72
Visceral metastases	Yes vs no	1.01 (0.64–1.62)	0.95
Bone metastases	Yes vs no	1.05 (0.57–1.95)	0.88
PSA	Log-transform, per 1 unit increase	1.10 (0.98–1.22)	0.10
Baseline albumin	Per 1 g dl^{-1} increase	0.56 (0.33–0.96)	0.036
NL ratio	Log-transform, per 1 unit increase	1.16 (0.87–1.54)	0.32
LDH	Elevated vs normal	2.85 (1.96–4.16)	<0.001
Hemoglobin	<11 vs ⩾11 g dl^{-1}	1.48 (0.94–2.31)	0.088
Prednisone	P vs no P	1.48 (1.03–2.13)	0.034
(b)			
Age	Per 10 years older	1.08 (0.81–1.45)	0.60
ECOG-PS	⩾1 vs 0	0.83 (0.50–1.38)	0.48
Gleason score	⩾8 vs ⩽7	1.57 (0.97–2.53)	0.065
Liver metastases	Yes vs no	1.34 (0.53–3.37)	0.54
Visceral metastases	Yes vs no	0.83 (0.44–1.56)	0.55
Bone metastases	Yes vs no	0.68 (0.30–1.52)	0.34
PSA	Log-transform, per 1 unit increase	1.15 (0.99–1.34)	0.069
Baseline albumin	Per 1 g dl^{-1} increase	0.83 (0.42–1.63)	0.59
NL ratio	Log-transform, per 1 unit increase	1.57 (1.08–2.27)	0.018
LDH	Elevated vs normal	2.03 (1.21–3.39)	0.007
Hemoglobin	<11 vs ⩾11 g dl^{-1}	1.11 (0.65–1.92)	0.70
Prednisone	P vs no P	2.28 (1.37–3.77)	0.001

Abbreviations: CI, confidence interval; ECOG-PS, Eastern Cooperative Group-Performance Status; LDH, lactate dehydrogenase; NL, neutrophil/lymphocyte; P, prednisone.

may be unmeasured systematic differences between these trials and it is impossible to distinguish between these potential differences, and differences due to treatment with P. Thus, the results require validation. Although the study could not identify a significant association of P with OS in univariable analyses, P was associated with higher grade ⩾3 toxicities in the multivariable analysis after controlling for major baseline prognostic factors. However, the results of the multivariable analysis are probably more relevant, as baseline clinical and tumor-related factors (for example, age, anemia, LDH and performance status) can affect both survival and toxicities.[14,17] Notably, the difference in toxicities does not imply lack of palliative benefits from corticosteroids that would require the longitudinal measures of quality of life using validated instruments. Given higher grade ⩾3 toxicities with P but not with placebo in those with LDH >ULN, high LDH may portend higher risk of toxicities from P. In addition, there were other significant differences between trials in terms of patients' characteristics. Data regarding corticosteroid use before trial and following start of trial therapy were not available, but may confound results and is another limitation. Nevertheless, most patients had probably been exposed to prior P, as they were all pretreated with docetaxel that is commonly administered in combination with P. Potentially, different results may have been obtained in patients not previously treated with P. The placebo was administered as a daily oral dose in the COU-AA-301 trial, and as 4 intravenous infusions given once every 3 weeks in the CA184-043 trial (nonprogressing patients could continue to receive infusions every 3 months till progression or toxicities). In addition, the CA184-03 trial administered a single 8 Gy dose of radiation to a bone metastasis at baseline (to enhance immune response to ipilimumab in the experimental arm), although this is unlikely to have affected either toxicities or survival in the placebo arm. However, both trials were conducted in post-docetaxel patients and control arms exhibited similar median OS (10–11 months) and progression-free survival (3–4 months).

Although corticosteroids are associated with toxicities as described earlier, daily-low dose corticosteroids appear to have modest antitumor activity and palliative benefits at least in a subset of patients, and may avert adverse effects of other antitumor agents. However, our study did not demonstrate differences in PSA declines between placebo and P. There may be differences based on the potency of the specific corticosteroid as suggested by a randomized phase II trial that demonstrated higher PSA response rates for dexamethasone vs prednisolone (47% vs 24%).[18] One setting where the use of daily oral corticosteroids is required is in combination with abiraterone, where corticosteroids inhibit mineralocorticoid excess leading to adverse events.[6,7] Corticosteroids may suppress adrenocorticotrophic hormone and downregulate androgens, cytokines and other growth-promoting factors.[19–23] The anti-inflammatory and anti-angiogenic activity of P may confer palliative benefits in 15 to 30% of patients, as demonstrated in prospective trials.[1,2,19–21,24,25] In pre-docetaxel patients, PSA and RECIST (Response Evaluation Criteria In Solid Tumors) responses were observed in 24% and 16% of patients receiving P, respectively.[6] Similarly, in post-docetaxel patients, PSA and RECIST responses were seen in 10.1% and 2.8% of patients, respectively.[26] Indeed, circulating tumor cell declines have been observed in a small subset of patients who received P alone.[27] One retrospective study of 200 patients with mCRPC suggested that P potentially extends progression-free survival in the context of docetaxel in patients with mCRPC (median progression-free survival 7.8 vs 6.2 months, $P=0.03$), although the benefit appeared limited to patients not previously exposed to corticosteroids.[28] Therefore, the clinical relevance of favorable PSA, RECIST, progression-free survival and circulating tumor cell changes and palliative benefits in a small subset of patients needs to be placed in the context of absence of evidence demonstrating improved OS.

In contrast, other data suggest a detrimental impact of corticosteroids on outcomes. Analysis of post-docetaxel men receiving enzalutamide demonstrated that corticosteroids at baseline were associated with worse survival.[29] The reason for this observation may be resistance mechanisms induced by enzalutamide or the institution of corticosteroids in patients with more aggressive symptomatic disease.[30] Preclinical data indicate that P exposure may foster resistance to androgen inhibitors by binding to glucocorticoid receptors.[9] It is also worrisome that corticosteroids may exhibit agonist activity on mutant androgen receptors.[31,32] In addition, lower testosterone appears to be associated with poorer survival, suggesting that lower testosterone mediated by corticosteroid-induced adrenocorticotrophic hormone suppression may mechanistically confer poorer outcomes.[33] Conversely, in post-docetaxel men receiving abiraterone plus P, baseline corticosteroids did not exhibit an impact on survival.[34]

Following the phase III trials using low-dose oral daily corticosteroids in combination with mitoxantrone, they were employed in combination with docetaxel or cabazitaxel, with the rationale being to maintain balance between the arms. However, randomized phase III trials evaluating enzalutamide, radium223, sipuleucel-T and ipilimumab contained control arms without P.[8,13,35–37] We propose that with the exception of the use of P with abiraterone to alleviate toxicities and single-agent P as late-line

palliative therapy in the absence of trials, its routine use should be restrained given absence of data demonstrating improved survival, and association with toxicities and resistance.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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